IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Selifonov *et al.*

Application No.: 09/618,579

Filed: July 18, 2000

Title: METHODS FOR MAKING CHARACTER STRINGS, POLYNUCLEOTIDES AND POLYPEPTIDES HAVING DESIRED CHARACTERISTICS

Attorney Docket No.: MXGNP001X3/124.610US

Examiner: Zhou, S.

Group: 1631

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APPEAL BRIEF TRANSMITTAL
(37 CFR 192)

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This brief is in furtherance of the Notice of Appeal filed in this case on May 7, 2004. This brief is transmitted in triplicate.

This application is on behalf of

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Respectfully submitted,
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

EX PARTE SELIFONOV *et al.*

Application for Patent

Filed: July 18, 2000

Serial No. 09/618,579

FOR:

METHODS FOR MAKING CHARACTER STRINGS, POLYNUCLEOTIDES AND POLYPEPTIDES HAVING DESIRED CHARACTERISTICS

APPEAL BRIEF

CERTIFICATE OF MAILING

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Signed: _____
Joyce Ferreira

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(1) REAL PARTY IN INTEREST

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(2) RELATED APPEALS AND INTERFERENCES

N/A

(3) STATUS OF CLAIMS

There are a total of 21 claims pending in this application (claims 139-159). Claims 1-138 have been cancelled. Claims 139-147 and 157-159 were examined and rejected. Claims 148-156 were withdrawn from consideration by the Examiner. The withdrawn claims are not involved in this appeal. However, they present essentially the same issues as the non-withdrawn claims. Appellants have strongly traversed the Examiner's restriction of these claims.

Claims 139-147 and 157-159 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent No. 6,403,312 issued June 11, 2002 to Dahiyat et al. (hereinafter the Dahiyat reference) in view of Venkatasubramanian et al., J. Chem. Inf. Comput. Sci. Vol. 35, pages 188-195, 1995 (hereinafter the Venkatasubramanian reference). There are no other rejections. The rejection of each of claims 139-147 and 157-159 under § 103 is appealed.

(4) STATUS OF AMENDMENTS

No amendment has been filed in response to the outstanding Office Action of November 7, 2003. All amendments previously filed on July 29, 2003 have been entered.

(5) SUMMARY OF INVENTION

All the claims on appeal are directed to methods of identifying a set of oligonucleotides for use in an *in vitro* recombination procedure. The sole independent claim on appeal recites the following four operations:

(a) providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides;

(b) computationally selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites;

(c) selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) computationally identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c).

Operation (a) of the claimed invention provides data identifying sequences of parental polypeptides or parental nucleic acids that encode the polypeptides. This is the context of the invention. See for example the bottom block in Figure 2, which references a "Library of Parental Strings" in one embodiment of this invention. Often the parental polypeptides or nucleic acids are represented as character strings encoding sequence information. See e.g., page 4, lines 8-17. Each character may represent a separate nucleotide or amino acid residue.

Operation (b) involves computationally selecting one or more cross-over sites on the parental sequences based on structural information about the associated polypeptides. This general concept and a few implementation examples are introduced at page 8, lines 1-28. See also page 74, line 28 to page 75, line 9. As indicated at page 8, the structural information employed may include information about structural motifs, structural co-variance, protein threading or folding information, stability analysis based on, e.g., energy minimization, etc. A further discussion of the relevant structural considerations is presented at page 48, lines 8 et seq. The concept as applied to nucleic acids is discussed at page 55, lines 27 to page 56, line 6, for example. Note that Figure 3 makes reference

to "crossover/recombination" genetic operators as well as a library of such operations. See the lower right-hand portion of Figure 3.

As suggested by the claim, the process of identifying cross-over sites in the parental sequences defines various recombinant polypeptides or nucleic acids resulting from joining sequence characters from different parents at the cross-over point. This is explained at page 17, lines 14-23. Note that this section of the specification describes the concept of cross-overs in terms of "hybrids" or "chimeras," which identify the resulting recombinant polypeptides or nucleic acids.

Operation (c) involves selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids. See e.g. page 76, lines 14-20. As an example of this operation in the context of the claimed invention, see page 77, line 28 to page 78, line 2, where recombinant nitric oxide synthases are computationally constructed and then analyzed for energy minimization, stability, etc.

Examples of techniques for assessing structural stability and other structural criteria relevant to operations (b) and (c) are set forth at page 54, lines 7-26 and at page 74, lines 14-17. It is important to note that the selection of cross-over sites based on structural information in (b) and the selection of recombinants by assessing structural stability in (c) can be the same operation. For example, an assessment of structural stability in parental polypeptides may be used to identify a cross-over point and also used, without more, to identify a stable recombinant selected from those produced by joining segments of the parent polypeptides at the cross-over point. See for example original claims 97 and 98.

Operation (d) is described at various locations in the specification. As mentioned, the operation involves computationally identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c). Relevant oligonucleotides are described at, for example, page 37, line 9 et seq. and at page 60, lines 18-23. As an example, operation (d) may be employed for identifying primers, see page 76, line 22 to page 77, line 6. In a specific embodiment, the operation can also be employed to identify bridging oligonucleotides (sequences including at least one cross-over point as well as some adjacent sequence regions on each side of the cross-over point). See page 82, line

7. An example of operation (d) is also presented in the lower left region of Figure 4 (including the block that reads "Define oligo size range, front/back overlap length . . . "). Further, some of the original claims recite examples of operation (d). See e.g., original claims 1, 12, 23, 93, and 94. For many applications of the claimed invention, at least one of the identified oligonucleotides represents a "bridging oligonucleotide" containing the cross-over site and sequence portions from two or more parents. See e.g., page 7, lines 14-27.

The invention as a whole is described generally elsewhere in the specification. For example, an embodiment of the invention is outlined at pages 73-82. Further, some aspects and examples of the presently claimed invention also appear in the originally submitted claims, particularly the claim sets associated with independent claims 1, 93, and 99.

One specific aspect of the invention provides that "the structural information employed in (b) comprises information depicting the three-dimensional structure of at least a portion of the parental polypeptides or polypeptides encoded by the parental nucleic acids." See claim 140. As indicated above, page 8 of the instant specification specifies that the structural information employed for this operation may include information about structural motifs, protein threading or folding information, etc. All of these depict the three-dimensional structure of at least a portion of the parental polypeptides. See also page 74, lines 6-12.

In a similar vein, certain aspects of the invention relate to selection of "cross-over points at sites that will preserve selected subunits, domains, or motifs in the parental polypeptides" or will "maintain or disrupt one ore more structural relationships between two or more amino acids in the parental polypeptides." See claims 142 and 143. These aspects are described at, for example, page 8, lines 1-28, page 48, lines 8-24, page 94, lines 22-29, and page 74, lines 6-14.

A related aspect of the invention specifies that "(c) comprises computationally assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids." See claim 147. This concept is presented at various locations and in various contexts. Examples of relevant passages include those found at page 54, lines 7-27, page 76, lines 16-20, page 77, line 28 to page 78, line 2, and at page 74, lines 6-12.

Another related aspect of the invention specifies that operation (b) "comprises selecting cross-over points that correspond to overlapping amino acids in the parental polypeptides." See claim 141. This feature is described at page 18, lines 13-16, for example. In addition, the invention may involve "aligning the two or more parental polypeptides or parental nucleic acids prior to computationally selecting one or more cross-over sites on the sequences." See claim 158. This feature appears in original claim 26, as well as claims 1 and 6, for example.

Other aspects of the invention pertain to "performing an additional genetic operation on one or more of the parental or recombinant polypeptides or the parental or recombinant nucleic acids." See e.g., page 20, lines 25-28, and, as a specific example, see page 17, lines 19-21. Examples of these additional genetic operations include multiplication, mutation, fragmentation, and ligation. See e.g., the discussion of genetic operations presented at pages 16 and 17. These features appear in claims 144 and 145.

Finally, various sources may provide the parent polypeptides or parental nucleic acids. In some embodiments, "the two or more parental polypeptides or parental nucleic acids comprise naturally occurring polypeptides or naturally occurring nucleic acids that encode polypeptides." See claim 146. This aspect of the invention is stated implicitly and explicitly throughout specification as originally filed. See e.g., original claim 103.

(6) ISSUES

The issues, which the Appellants believe to be most pertinent to the present appeal, include:

A) Whether the Dahiyat et al. and Venkatasubramanian et al. references together describe or suggest to one of skill in the art ". . . *(b) computationally selecting one or more cross-over sites on the sequences . . .; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites*" and can thereby render the claims on appeal unpatentable under 35 USC 103. (Claims 139-147 and 157-159 – see operation (b) of claim 139)

B) Whether the Dahiyat et al. and Venkatasubramanian et al. references together describe or suggest to one of skill in the art ". . . *(a) providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides*" and can thereby render the claims on appeal unpatentable under 35 USC 103. (Claims 139-147 and 157-159 – see operation (a) of claim 139)

C) Whether the Dahiyat et al. and Venkatasubramanian et al. references together describe or suggest to one of skill in the art ". . . *(c) selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids*" and can thereby render the claims on appeal unpatentable under 35 USC 103. (Claims 139-147 and 157-159 – see operation (c) of claim 139)

D) Whether the Dahiyat et al. and Venkatasubramanian et al. references together describe or suggest to one of skill in the art the additional features recited in the

dependent claims and can thereby render each claim dependent unpatentable under 35 USC 103. (Claims 140-147 and 157-159)

(7) GROUPING OF THE CLAIMS

The rejected claims do not stand or fall together, and will be argued separately. The following claim groups will be argued separately. Each of the appealed claims 139-147 and 157-159 is separately patentable and reasons explaining the separate patentability are presented below.

(8) ARGUMENTS

Introduction And Summary

Claims 139-147 and 157-159 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Dahiyat in view of Venkatasubramanian. The Appellants' explanation of the differences between the above-cited references and the claimed invention will first be discussed for claim 139, and then for each of the dependent claims.

Both Dahiyat and Venkatasubramanian describe computational methods for identifying new compositions. Dahiyat's method begins with a single peptide sequence, which is referred to as a "scaffold." The methodology introduces point mutations in the scaffold at identified amino acid residues to thereby define a "primary library." Then combinations of these mutations are selected to generate a "secondary library." Fundamentally, all members of each library trace their lineage back to the single scaffold.

Venkatasubramanian's method selects repeat units for bulk industrial polymers (plastics). Various polymer mainchain and sidechain groups are present in a seed population, and these are manipulated to produce new repeat units. The manipulations include insertion and deletions of mainchain and sidechain groups, random mutations of these groups, "hops" among the groups, and crossover operations.

As indicated, claim 139 recites the following operations:

(a) providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides;

(b) computationally selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites;

(c) selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) computationally identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c).

Among other distinctions from the claimed invention, Dahiyat does not select or use a cross-over operation. In fact, it cannot accomplish this, at least in the manner claimed, because it does not employ two or more parental polypeptides or nucleic acids.

Among other distinctions from the claimed invention, the Venkatasubramanian method does not pertain to polypeptides or nucleic acids. It also does not select cross-over sites based on structural information about parental sequences. It selects them randomly. Nor does it pertain to *in vitro* recombination.

The combination of Dahiyat and Venkatasubramanian would not lead one of skill in the art to the claimed invention. To reach the claimed invention from these references would require too many leaps. It would also require too many special choices such as which operations to use, how to apply them, and how to arrange them sequentially. Reaching the claimed invention from Dahiyat and Venkatasubramanian could only be accomplished by using the invention as a template and then picking and choosing select features from these references and cobbling them together in a wholly unexpected manner.

Dahiyat's entire discussion, including all of its examples, is premised on a single scaffold starting point. To graft the claimed cross-over operation to Dahiyat's

methodology, one must first replace Dahiyat's single scaffold starting point with a two parental polypeptide starting point. Then one must identify cross-over points in the two parental polypeptides and perform recombination as claimed. How would one go about locating such cross-over sites? The claims specify that these sites are selected using structural information about the parent sequences. Instead of doing this, one of skill might more naturally place them randomly, as is done in the Venkatasubramanian method.

Venkatasubramanian does not provide the necessary motivation to recast Dahiyat's methodology so as to arrive at the claims. Yes, Venkatasubramanian does identify cross-over and other operators as applied to industrial plastics, but why would one of skill in the art even consider integrating parts of Venkatasubramanian's approach into Dahiyat's method when Dahiyat does not employ two or more parental sequences. And even if one would be motivated to integrate pieces of Venkatasubramanian into Dahiyat's methodology, how would one go about it? Rather than employing two parental polypeptides or nucleic acids, as recited in the claims, the cited references more likely incorporate Venkatasubramanian's crossover on the single parent scaffold to create a rearranged scaffold. This combination of Dahiyat and Venkatasubramanian falls well outside the claims. Further, how would one select cross-over points in a method constructed from a combination of Dahiyat and Venkatasubramanian? Venkatasubramanian does this randomly. The claims require more.

The References

It will be useful to further discuss the two cited references.

Dahiyat

The Dahiyat et al. patent describes a computational method of introducing diversity in a "scaffold" peptide sequence by identifying specific amino acid residues for variation. The starting point for the process is a single "scaffold" sequence. Column 5, line 16 to column 6, line 46. Mutations in this scaffold at the identified residues are selected for a "primary library." Column 6, line 47 to column 14, line 39. Then combinations of these mutations are selected in various sequences to generate a secondary library. Column 14, line 40 to column 16, line 28. Each of these steps,

including generation of the secondary library, is performed computationally. Dahiyat et al. describe no other computational techniques of relevance.

According to Dahiyat et al., the members of the secondary library may be synthesized by various techniques. Column 16, line 42 to column 18, line 17. Some of these involve multiple PCR reactions using oligonucleotides. One specific example is gene shuffling with error prone PCR. See column 17, lines 53-67. These processes employ overlapping oligonucleotides, which correspond to the full-length gene (scaffold). Column 16, lines 64-65. The oligonucleotides encode the variant amino acids introduced to the scaffold in the primary or secondary library (which were identified by computation). In some cases, there is a single variant amino acid in each oligonucleotide. See e.g., column 17, lines 17-19.

Example 1 in Dahiyat presents the methodology more concretely. It describes a procedure for making and computationally screening an array of mutant polypeptides of β-lactamase TEM-1. As illustrated in Example 1, the computational stage of the process identifies five different positions on a single scaffold protein for amino acid variation. The specific amino acids chosen for each of these positions are set forth in Table 4. In the *in vitro* stage of the process, 210 sequences corresponding to combinations of the five point mutations in the scaffold protein (TEM-1 gene for β-lactamase) are generated from oligonucleotides encoding the amino acid variations at the five sites.

The computational source of diversity in the Dahiyat patent is limited to specific residue mutations within a scaffold. These are essentially point mutations. The Dahiyat method provides a framework for selecting scaffold residues to vary and for choosing specific variations based on biochemical principles of the stability and activity. In the end, all the olignucleotides trace their sequences to a single scaffold and the amino acid variations computationally generated to produce the primary library. These oligonucleotides did not originate from multiple parent sequences.

Venkatasubramanian

Venkatasubramanian describes a genetic algorithm for identifying a repeat unit of a bulk industrial plastic such as polyethylene terephthalate (PET), polyvinylidene propylene copolymer, polycarbonate of bisphenol-A, and the like. In the genetic algorithm, various mainchain groups (>C<, -S-, -O-(C=O)-, -NH-, -(C=O)-NH-, phenyl

based groups, complete monomer units, etc.) and sidechain groups (-H, -CH_3, -Cl, -CN, -O-(C=O)-OCH_3, etc.) are brought together to create the repeat units under consideration. Repeat units are generally comprised of 2 to 10 mainchain groups strung together in a defined sequence. Sidechain selections may contribute to the identity of the repeat unit.

These mainchain and sidechain groups are present in seed population, and are manipulated to produce next generation repeat units by applying various *operators* identified at page 190. Crossover is among the operators used by Venkatasubramanian et al. in their study. Other operators identified as potential sources of manipulation include insertions, deletions, point mutations, hops, and blends, each of which may be applied to the mainchain or sidechain. A fitness function selects particular repeat units in each generation to be used in a succeeding generation. The fitness function selects these repeat units on the basis of various materials properties such as density, glass transition temperature, thermal expansion coefficient, specific heat capacity, and bulk modulus. See page 191, left column. Also, the fitness function automatically rejects sequences deemed to be chemically unstable and therefore unrealistic. Named examples were –O-O-O- and OC=O-C=O-.

Regarding the claimed invention, the Venkatasubramanian genetic algorithm is not concerned with nucleotide or peptide applications. Therefore, its character strings do not represent "two or more parental polypeptides or parental nucleic acids that encode the polypeptides" and it does not computationally identify "one or more oligonucleotides for *in vitro* recombination."

Nor does it describe "computationally selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids". Venkatasubramanian's crossover sites were identified randomly. See page 190, left column, where it is pointed out that "the cutting position is randomly chosen for both parents."

Recent Prosecution

With respect to issue A, the claims at issue specify a method of identifying a set of oligonucleotides for use in an *in vitro* recombination procedure. As mentioned, the method involves various computational operations performed on data that identifies

sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides. Of relevance to the discussion of issue A, the method operations include

> . . . (b) computationally selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites.

Previously, the Examiner argued that the cross-over feature (along with each additional claim element) was disclosed in the Dahiyat reference. See the Office Action mailed January 29, 2003. In the most recent Office Action, the Examiner backed off from this position and brought in the Venkatasubramanian reference to address the cross-over feature of the claims. The Examiner's current position is explained at page 3 of the most recent Office Action:

> Dahiyat et al. do not explicitly recite the term "crossover" as required in the instant claims.
>
> Venkatasubramanian et al. discloses a computational method of designing new chemical polymers using a genetic algorithm. The method comprises providing two mating parents of a chemical polymer and manipulating the mating parents using such genetic operators as crossover and mutation to produce derivative chemical polymers with desired properties. See page 188, right column, bottom paragraph and page 189, left column. Venkatasubramanian et al. also discuss recombination of nucleic acids (see page 189, left column).

Appellants dispute this last point and will address it later in this section. Appellants also dispute the implicit assumption that Dahiyat only requires the concept of "cross-over" and it otherwise suggests the claimed invention.

The Combination of Dahiyat and Venkatasubramanian Does Not Suggest the Claimed Invention

Fundamentally the concept of a chimeric sequence comprised of sequences from two parents and joined at a crossover point is lacking in Dahiyat. As the primary reference, Dahiyat requires more modification than can be supplied by Venkatasubramanian. Dahiyat does not come close to the claimed invention.

Admittedly Dahiyat's method does generate new peptide sequences by computationally modifying the scaffold sequence. And it does employ computational methods to predict structural stability of mutated peptide sequences. But it does not employ any source of diversity other than point mutations. It does not employ two parental sequences. Therefore it cannot suggest any operation resembling cross-over. Nor can it suggest any process which selects cross-over sites based on "structural information about the parental polypeptide or polypeptides encoded by the parental nucleic acids."

Assuming for the sake of argument that Venkatasubramanian describes a cross-over operation that falls within the meaning of that term in the claimed invention, Venkatasubramanian still cannot supply the features that are lacking in Dahiyat. Simply importing the concept of a cross-over operation to Dahiyat's method will not meet the claim limitations. Neither reference points to the need to select cross-over sites based on information about the parental sequences. Venkatasubramanian chooses cross-over sites randomly.

And even if one assumes for the sake of argument that Dahiyat and Venkatasubramanian together disclose all elements of the claimed invention, neither reference suggests any particular way to incorporate cross-over in a hybrid process. Because the methods described in Venkatasubramanian and Dahiyat are so different and because each employs a number of steps, it is far from clear that one of skill in the art reviewing these to references would put them together to produce a hybrid method that is anywhere near the claimed invention. How exactly would one of skill in the art integrate Venkatasubramanian's cross-over operation with the Dahiyat method? There are several ways this could be done, with most or all of them falling outside the scope of the pending claims.

For example, one way to import the concept of cross-over to Dahiyat's method involves performing cross-over on Dahiyat's single parent template. While this would result in a rearrangement of the scaffold sequence, it would not produce a "recombinant" polypeptide derived from two or more parental polypeptides. Hence this hybrid method of Dahiyat and Venkatasubramanian would not fall within the scope of the claims. Another way to combine the Dahiyat and Venkatasubramanian methods involves performing random cross-over on short repeat units of Dahiyat's template. Note that Venkatasubramanian employs random crossover on polymer repeat units of 2 to 10 mainchain units in length (e.g., $[-CH_2-CF_2-CH_2-CHCH_3-]_n$). This hybrid method also falls outside the claim scope. Many other hybrid methods outside the claim scope also result from combining the two references.

To produce a method reasonably close to Appellant's claimed method, one must first invent a second parental polypeptide sequence for Dahiyat. One must also invent a way to select the cross-over point non-randomly. Thus, it is not enough to simply graft the notion of a cross-over from Venkatasubramanian to Dahiyat.

As a matter of law, features of cited prior art references must be applied in their proper context. One cannot take a first feature associated with one function of a prior art reference and replace it with a second feature from a different reference (or even from the same reference) but associated with wholly different function. It would be improper to transpose Venkatasubramanian's discussion of cross-over in polymer repeat units to Dahiyat's discussion of point mutations in a single scaffold of polypeptide sequence – unless there was some teaching to suggest this substitution. It is respectfully submitted that no such suggestion exists in Dahiyat or Venkatasubramanian.

At the core of this issue, there is no real motivation for one of skill to combine the methods of Venkatasubramanian and Dahiyat. The two references present fundamentally different algorithms and apply their algorithms to significantly different materials. Venkatasubramanian's method operates on short repeat units of bulk polymers and explores comparatively wide regions of polymer space. Dahiyat's method operates on much longer polypeptides and explores comparatively limited regions of the available sequence space (in an effort to preserve conformations, etc.). And again Dahiyat's disclosure is based entirely on a single scaffold starting point. A cross-over operation is not feasible or relevant in this context.

Venkatasubramanian Does Not Disclose Nucleic Acids/Peptides

It is important to bear in mind that Venkatasubramanian does not discuss polypeptides or nucleic acids. Instead Venkatasubramanian acts on short repeatable segments of bulk polymer plastics. These segments have lengths of 2-10 main-chain units. The main chain units are shown in Table 1 on page 190 (e.g., >C<, -S-, SO_2-, -C_6H_4-, -C=OO-, -NH-, -C=ONH-, and -O-). Side chains are also varied in some cases. The authors were looking for novel main-chain arrangements providing improved bulk properties (density, glass transition temperature, thermal expansion coefficient, specific heat capacity, and bulk modulus). In contrast, the field of Dahiyat's method is directed evolution of proteins. Proteins are much larger molecules, usually selected for a biological activity such as enzyme activity.

Appellants note that the Examiner has stated that "Venkatasubramanian et al. also discuss recombination of nucleic acids (see page 189, left column)." However this is not the case. The reference does indicate that the genetic operators such as mutation and cross-over are applied to "genes" (see page 189 as cited). But the entire discussion in this regard is an overview of "genetic algorithms." These are algorithms that mimic evolution and natural selection, but do not intrinsically act on nucleic acids. They are intended to explore a wide range of possibilities in a search that gradually leads to one or a few "fit" solutions. Genetic algorithms are commonly applied to financial problems, scheduling applications, composite material design, mobile communications infrastructure optimization, etc. In Venkatasubramanian, a genetic algorithm is employed to explore many possible sub-units for industrial polymers. Venkatasubramanian's disclosed application has nothing to do with manipulations of nucleic acids or polypeptides.

It should also be noted that because Venkatasubramanian's genetic algorithm is not concerned with nucleotide or peptide applications, it does not computationally identify "one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c)." See operation (d) of claim 139.

Dahiyat's Mutations Are Not Crossover Operations

As pointed out, Dahiyat does not suggest a cross-over operation. Appellants note however that in a previous Office Action, the Examiner made the following argument as

to why the Dahiyat patent renders the elected claims obvious, even though it does describe "crossover":

> While Dahiyat et al. do not explicitly recite the term "crossover" as required by the instant claims, and do not explicitly indicate this procedure for generating recombinant sequences, the fact that particular sites are selected and allowed to change to other amino acid residues in order to generate mutant proteins would have made it obvious to an ordinary person in the art that those sites would have served as crossover sites, the wild type sequence and those with other amino acid residues at one particular position selected would have been parental sequences, and the resultant mutant sequences which would have different amino acid residues at all those positions selected would have been recombinants. Page 4 of the January 29, 2003 Office Action.

The Appellants have disputed this contention in response to the earlier Office Action. First, it is not seen how the sites selected by the Dahiyat authors for changing amino acids "would have served as crossover sites." A crossover site generally represents the interface between segments of two different parent sequences. It is the point where the segments are joined. Choosing an amino acid position for variation within a scaffold template does not serve to define a crossover point for joining segments from two different parents.

Second, it appears from the Examiner's remaining remarks that he possibly viewed the scaffold as one parent ("wild type sequence") and the single amino acid variation for the site in question as originating with a second, undisclosed, parent. It is submitted that such reading is inconsistent with the well-understood meaning cross-over.

In the specification, cross-over is described as follows:

> CROSSOVER (RECOMBINATION)- This operator formally comprises joining a continuous part of one string with a continuous part of another string in such a way that one or two hybrid strings are formed (chimeras), where each of the chimeras contain at least two connected continuous string areas each comprising partial sequence of two different recombining strings. The area/point where sequence characters from different parental strings, is termed the crossover/recombination area/point. Page 17, lines 14-19.

As is consistent with the common meaning of crossover, this description specifies that *continuous* portions of two separate sequences (strings) are joined. A single variant amino acid inserted into scaffold sequence would not be viewed by one of skill in the art as a continuous portion of a sequence.

It is also respectfully submitted that, contrary to the Examiner's earlier assertion, the Dahiyat patent does not suggest a second parent as the source of the replacement amino acid residue at the selected position. Dahiyat describes a computational methodology for choosing such replacement amino acids. That methodology in no way relies on a "parent" sequence or obtaining a partial sequence of a parent sequence. In Dahiyat, there is no parent for the replacement amino acids.

Issues B and C

While the above arguments focus on Issue (A), which relates to element (b) of claim 139, aspects of the arguments also pertain to Issues (B) and (C). Thus, to some degree, the arguments regarding issues (A)-(C) collapse into a single position. However, it is nevertheless worth pointing out that when considered in isolation, the claim elements specified in Issues (B) and (C) present distinctly patentable features.

Issue (B) pertains to the claim element of "*providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides*" As indicated, the Venkatasubramanian reference is concerned with repeat units for bulk industrial polymers such as PET and bisphenol-A. It in no way suggests providing parental polypeptides or nucleic acids. And while the Dahiyat reference does pertain to polypeptides, it provides only a single scaffold peptide for all its mutations. Two parental sequences are nowhere suggested in Dahiyat. Therefore recited element (a) of claim 139 is not presented by the cited references and the appealed claims are patentable for this reason alone.

Issue (C) pertains to element (c) of claim 139:

> *selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids . . . .*

Because neither the method of Dahiyat nor the method of Venkatasubramanian provide recombinant polypeptides or recombinant nucleic acids produced from cross-over of two parental polypeptides or nucleic acids, this element of claim 139 is also not met. Therefore recited element (c) of claim 139 is not presented by the cited references and the appealed claims are patentable for this reason alone.

Issue D

As indicated above all appealed claims are separately patentable over the cited references. Each dependent claim recites an additional limitation that is not found in the cited art.

Claim 140 specifies that "the structural information employed in (b) comprises information depicting the three-dimensional structure of at least a portion of the parental polypeptides or polypeptides encoded by the parental nucleic acids." While Dahiyat may disclose methods that consider the three-dimensional structure of polypeptide, it is most certainly not for the purpose of selecting a cross-over site. See operation (b) of claim 139. Nor does it pertain to multiple parental polypeptides. Further, to the extent that the three-dimensional structure of at least a portion of a polypeptide is considered relevant to the combination of Dahiyat and Venkatasubramanian, any suggestion to combine them in the manner claimed becomes even more tenuous. Venkatasubramanian considers only the linear structure of its repeat units. It has nothing to do with three-dimensional structures. Further, as noted, it selects cross-over sites randomly. A *prima facie* case of obviousness has not been made for claim 140. Reversal of the rejection is requested.

Claim 141 specifies that operation (b) "comprises selecting cross-over points that correspond to overlapping amino acids in the parental polypeptides." Venkatasubramanian selects cross-over points randomly. Dahiyat does not even select cross-over points. The need to select cross-over points at positions corresponding to overlapping amino acids in parental polypeptides is not remotely suggested in either reference. As the feature separately recited in claim 141 is remote from the cited references, the claim is separately patentable over the cited art. A *prima facie* case of obviousness has not been made. Reversal of the rejection is earnestly solicited.

Claim 142 specifies that operation (b) "comprises selecting cross-over points at sites that will preserve selected subunits, domains, or motifs in the parental polypeptides." Assuming for the sake of argument that Dahiyat considers preservation of at least one of subunits, domains, or motifs relevant, such preservation is not for the purpose of selecting a cross-over sites for sequences of multiple parental polypeptides. Further, a workable combination of the Venkatasubramanian and Dahiyat methods becomes even more remote. Again Venkatasubramanian chooses cross-over sites randomly. A *prima facie* case of obviousness has not been made for claim 142. Reversal of the rejection is requested.

Claim 143 further specifies that operation (b) "comprises selecting cross-over points at sites chosen to maintain or disrupt one or more structural relationships between two or more amino acids in the parental polypeptides." This feature is nowhere suggested in the cited references. A separate *prima facie* case of obviousness has not been made for claim 143. Reversal of the rejection is requested.

Claim 144 recites that the method of claim 139 additional comprises "performing an additional genetic operation on one or more of the parental or recombinant polypeptides or the parental or recombinant nucleic acids." Dahiyat performs only point mutations. The concept of performing both cross-over and some other operation is not suggested. Even if one were to conclude that the Dahiyat's point mutations on a scaffold peptide could be replaced with a cross-over operation on two parental polypeptides, it requires a greater leap to conclude that one should additionally perform a second genetic operation on the scaffold or recombinant polypeptides. Thus, a separate *prima facie* case of obviousness has not been made for claim 144. Reversal of the rejection is requested.

Claim 145 depends from claim 144 and specifies that the genetic operation of claim 144 is selected from the group "multiplication, mutation, fragmentation, and ligation." If one were to conclude that claim 144 is suggested by the prior art, it requires a further leap to conclude that the prior art specifies a combination of cross-over and one of these additional genetic operations be performed on a parental or recombinant polypeptide. Thus, a separate *prima facie* case of obviousness has not been made for claim 145. Reversal of the rejection is requested.

Claim 146 recites that "two or more parental polypeptides or parental nucleic acids comprise naturally occurring polypeptides or naturally occurring nucleic acids that encodes polypeptides." As Venkatasubramanian does not suggest to polypeptides or

nucleic acids of any sort, it even more clearly does not suggest naturally occurring versions of these. And while some examples presented in the Dahiyat patent may pertain to naturally occurring polypeptide scaffolds, the recitation of claim 146 that *two or more* of the parental polypeptides be naturally occurring requires a greater leap than requiring only that Dahiyat replace its single scaffold with two or more parental polypeptides. Thus, claim 146 presents a separate ground for patentability. Reversal of the rejection is requested.

Claim 147 recites that operation (c) "comprises computationally assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids." While Dahiyat may disclose methods that consider the three-dimensional structure and possibly even the three-dimensional structural stability of polypeptide, it is most certainly not for the purpose of selecting recombinant polypeptides produced from cross-over of two or more parents. Further, to the extent that the three-dimensional structure of at least a portion of a polypeptide is considered relevant to the combination of Dahiyat and Venkatasubramanian, any suggestion to combine them in the manner claimed becomes even more tenuous. Venkatasubramanian considers only the linear structure of its repeat units. It has nothing to do with three-dimensional structures. A *prima facie* case of obviousness has not been made for claim 147. Reversal of the rejection is requested.

Claim 157 recites that "the oligonucleotides identified in (d) are "bridging" oligonucleotides." This recitation decreases the likelihood that a combination of Venkatasubramanian and Dahiyat would suggest the claimed invention. Again, Venkatasubramanian has nothing to do with identifying one or more oligonucleotides for *in vitro* recombination. To specify such oligonucleotides are bridging oligonucleotides presents an additional feature that must be derived from Dahiyat. As Dahiyat does not employ cross-over, the concept of a bridging oligonucleotide is far from suggested. A *prima facie* case of obviousness has not been made for claim 157. Reversal of the rejection is requested.

Claim 158 recites the additional operation of "aligning the two or more parental polypeptides or parental nucleic acids prior to computationally selecting one or more cross-over sites on the sequences." This limitation is nowhere suggested in either cited reference. Reversal of the rejection is the rejection is requested.

Finally, claim 159 recites that "the recombinant polypeptides or recombinant nucleic acids that result from the cross-overs comprise contiguous sequences of multiple amino acids or nucleotides from the two or more of the parental polypeptides or parental nucleic acids." As Venkatasubramanian is not concerned with polypeptides or nucleic acids and Dahiyat is not concerned with cross-over operations, this operation is not suggested. To the extent that Dahiyat's point mutations would be viewed by the PTO to be a form of cross-over, this claim should clarify that the operations are very distinct. A *prima facie* case of obviousness has not been made for claim 159. Reversal of the rejection is requested.

Conclusion

Appellants have pointed out that the cited references contain insufficient teachings to render the claims *prima facie* obvious. In combination, the references fail to suggest a method of cross-over two or more parental polypeptides or nucleic acids as claimed, without using the claims as a blueprint and recasting one or both of the reference's to something wholly unrelated to its original form. In order for the cited references to render the claims obvious, at least one of the references would have had to teach one of skill to select a cross-over site by some methodology other random selection. Further, at least one of the references would have to show use of two or more parental polypeptide or nucleic acid sequences for cross-over.

In view of the foregoing, it is respectfully submitted that none of the pending claims are rendered unpatentable by the Venkatasubramanian and Dahiyat references. Accordingly, the pending rejections of all of the claims under 35 U.S.C. § 103 should be reversed.

Respectfully submitted,
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(9) APPENDIX

APPENDIX
PENDING CLAIMS

1-138 (canceled)

139. (previously presented) A method of identifying a set of oligonucleotides for use in an *in vitro* recombination procedure, the method comprising:

(a) providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides;

(b) computationally selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites;

(c) selecting at least one of the recombinant polypeptides or recombinant nucleic acids by computationally assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) computationally identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c).

140. (previously presented) The method of claim 139, wherein the structural information employed in (b) comprises information depicting the three-dimensional

structure of at least a portion of the parental polypeptides or polypeptides encoded by the parental nucleic acids.

141. (previously presented) The method of claim 139, wherein (b) comprises selecting cross-over points that correspond to overlapping amino acids in the parental polypeptides.

142. (previously presented) The method of claim 139, wherein (b) comprises selecting cross-over points at sites that will preserve selected subunits, domains, or motifs in the parental polypeptides.

143. (previously presented) The method of claim 139, wherein (b) comprises selecting cross-over points at sites chosen to maintain or disrupt one ore more structural relationships between two or more amino acids in the parental polypeptides.

144. (previously presented) The method of claim 139, further comprising performing an additional genetic operation on one or more of the parental or recombinant polypeptides or the parental or recombinant nucleic acids.

145. (previously presented) The method of claim 144, wherein the genetic operation is selected from the group consisting of multiplication, mutation, fragmentation, and ligation.

146. (previously presented) The method of claim 139, wherein the two or more parental polypeptides or parental nucleic acids comprise naturally occurring polypeptides or naturally occurring nucleic acids that encodes polypeptides.

147. (previously presented) The method of claim 139, wherein (c) comprises computationally assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids.

148. (Withdrawn) A computer program product comprising a machine readable medium on which is provided program instructions for identifying a set of oligonucleotides for use in an *in vitro* recombination procedure, the program instructions comprising:

(a) code for providing data identifying sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides;

(b) code for selecting one or more cross-over sites on the sequences based on structural information about the parental polypeptides or polypeptides encoded by the parental nucleic acids; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites;

(c) code for selecting at least one of the recombinant polypeptides or recombinant nucleic acids by assessing structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids; and

(d) code for identifying one or more oligonucleotides for *in vitro* recombination by choosing at least one portion of at least one of the recombinant polypeptides or recombinant nucleic acids selected in (c).

149. (Withdrawn) The computer program product of claim 148, wherein the structural information employed in (b) comprises information depicting the three-dimensional structure of at least a portion of the parental polypeptides or polypeptides encoded by the parental nucleic acids.

150. (Withdrawn) The computer program product of claim 148, wherein (b) comprises code for selecting cross-over points that correspond to overlapping amino acids in the parental polypeptides.

151. (Withdrawn) The computer program product of claim 148, wherein (b) comprises code for selecting cross-over points at sites that will preserve selected subunits, domains, or motifs in the parental polypeptides.

152. (Withdrawn) The computer program product of claim 148, wherein (b) comprises code for selecting cross-over points at sites chosen to maintain or disrupt one ore more structural relationships between two or more amino acids in the parental polypeptides.

153. (Withdrawn) The computer program of claim 148, further comprising code for performing an additional genetic operation on one or more of the parental or recombinant polypeptides or the parental or recombinant nucleic acids.

154. (Withdrawn) The computer program product of claim 153, wherein the genetic operation is selected from the group consisting of multiplication, mutation, fragmentation, and ligation.

155. (Withdrawn) The computer program product of claim 148, wherein at least one of the parental polypeptides or the parental nucleic acids comprise a naturally occurring polypeptide or a naturally occurring nucleic acid that encodes a polypeptide.

156. (Withdrawn) The computer program product of claim 148, wherein (c) comprises code for assessing three-dimensional structural stability of at least some of the recombinant polypeptides or polypeptides encoded by the recombinant nucleic acids.

157. (previously presented) The method of claim 139, wherein the oligonucleotides identified in (d) are "bridging" oligonucleotides.

158. (previously presented) The method of claim 139, further comprising aligning the two or more parental polypeptides or parental nucleic acids prior to computationally selecting one or more cross-over sites on the sequences.

159. (previously presented) The method of claim 139, wherein the recombinant polypeptides or recombinant nucleic acids that result from the cross-overs comprise contiguous sequences of multiple amino acids or nucleotides from the two or more of the parental polypeptides or parental nucleic acids.